REMARKS

The Office Action mailed July 6, 2010, was reviewed and the comments of the Patent and Trademark Office were considered. As of the last amendment, claims 1-10 and 12-42 are pending and 1, 2, 8, 16 and 27-34 were withdrawn from consideration. By this response, claims 3, 7-9, 15, 24, 41 and 42 are amended and claims 4 and 6 are cancelled. No new matter has been added by this Amendment. Support for the amendment can be found generally in the original claims and specification.

The specification and claims have further been amended to correct [GH] to [HG]. The specification and claims as filed had a formula with [GH] group, and have been corrected to [HG]. Support can be found at page 6, [0115] and page 7, [0131].

Rejection of claims under 35 U.S.C. § 112, second paragraph

Applicants kindly thank the Examiner for withdrawing the rejection of claim 7. The Examiner currently rejects claim 24 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. The applicant amended this claim in order to overcome this issue and therefore respectfully requests the Examiner withdraws the rejection of claim 24 as being indefinite under 35 U.S.C. § 112, second paragraph.

Rejection of claims under 35 U.S.C. § 112, first paragraph-enablement

The Examiner rejects claims 3-7, 9, 10, 12-15, 17-26 and 35-42 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make or use the invention commensurate in scope with the claims. Specifically, the Examiner alleges that the specification, while being enabling for an interleukin formulation comprising a polyglutamate polymer grafted with α-tocopherol which spontaneously associates with bovine serum albumin to form a gel *in vitro* in a concentration-dependent manner, does not reasonably provide enablement for the claimed super-genus of structural variants comprising at least one active principle (AP) and a biodegradable polymer (PO) carrying hydrophobic groups (GH).

Applicants have amended claim 3 to add limitation of interleukin, recite the type of polymer (PO) and recite the critical concentration for which a gelled deposit is observed *in vitro* in an IG test. Amended claim 3 is to:

> A liquid pharmaceutical formulation for the prolonged release of **interleukin(s),**
>
> wherein said formulation is liquid in the ambient atmosphere and is liquid at physiological temperatures, at physiological pH, in the presence of a physiological electrolyte in a physiological concentration, or in the presence of at least one surfactant, and
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> wherein said formulation comprises an aqueous colloidal suspension of low viscosity comprising submicronic particles of water - soluble biodegradable polymer PO,
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> wherein said submicronic particles are non - covalently associated with **the interleukin(s)**, and
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> wherein the dispersion medium of the aqueous colloidal suspension of low viscosity consists consisting essentially of water, and
>
> wherein the **polymer PO is a polyamino acid comprising aspartic units, glutamic units, or both aspartic and glutamic units, wherein at least one of said unit carries at least one graft comprising at least one hydrophobic group (GH) selected from the group consisting of α-tocopherol, cholesterol and n-dodecanol** wherein the **concentration of PO is greater than or equal to 0.9 C1** where C1 is the "induced gelling" concentration of the particles of PO, as measured in an IG test.

(emphasis added). As such, Applicants respectfully request the rejection to claim3 be withdrawn.

Further, at page 5 of the office action, the Examiner argues that neither the claim 23 nor the claim 24 limit the other generic components of the composition including the water-soluble biodegradables polymer PO, surfactants, or physiological electrolytes. The applicant amended the claim 3 in order to specify the water-soluble polymer PO, which is a polyamino acid comprising aspartic units, glutamic units or both aspartic and glutamic units.

Concerning the surfactants or the physiological electrolytes, these compounds <u>are not part of the composition</u>. The composition contains a polymer PO, an interleukin and optionally another active principle. Because this formulation is further injected, it <u>has to be liquid</u> under the conditions described in claim 3, namely "in the ambient atmosphere, at physiological temperatures, at physiological pH, in the presence of a physiological electrolyte in a physiological concentration, or in the presence of at least one surfactant". Therefore physiological electrolytes and surfactants are part of the conditions for which the composition

has to be liquid, but are not included in the composition itself. Accordingly, the applicants respectfully request the Examiner withdraw this rejection.

Rejection of claims under 35 U.S.C. § 112, first paragraph – written description

The Examiner rejects claims 3-7, 9, 10, 12-15, 17-26 and 35-42 under 35 U.S.C. § 112, first paragraph, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicants have amended the claims to illustrate the active principle is interleukin, the polymer PO is a polyamino acid comprising aspartic units, glutamic units, or both aspartic and glutamic units, wherein at least one of said unit carries at least one graft comprising at least one hydrophobic group (GH) selected from the group consisting of α-tocopherol, cholesterol and n-dodecanol, and the concentration of PO is greater than or equal to 0.9 C1 where C1 is the "induced gelling" concentration. The specification clearly notes that the inventors had possession of this invention. See, for instance, Examples 1-8 illustrating polyaminoacids with alpha-tocopherol (P1, P2, P3), cholesterol (P4, P5) and n-dodecanol (P6) where the active principle is an interleukin. Accordingly, the applicants respectfully request the Examiner withdraw this rejection.

Rejection of claims under 35 U.S.C. § 103

The Examiner rejects claims 3-7, 9, 10, 12-15, 17-26, and 35-42 under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO00/30618 ("Huille"), U.S. Patent No. 7,030,155 ("Lambert") and U.S. Patent No. 5,102,872 ("Singh") as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi *et al.* (*J. Controlled Release*, 1998; 54:313-320). Applicants traverse this rejection.

The main objective of the current invention is to find a formulation allowing an increased prolonged release time of interleukin, such that this release time is beyond 24h after administration *in vivo*. This objective is achieved by determining the critical concentration of the polymer PO in a specific IG test developed by the applicant (See specification at page 5, [0096]).

Huille (the '171 patent) discloses delivery particles based upon linear amphiphillic polyamino acids with α - peptide chains. See, the '171 patent at Abstract. Huille does neither

mention nor suggest a critical concentration of polymer greater or equal to 0.9 C1. This prior art does also not disclose such a specific test to determine the concentration C1. This is to the applicant's credit to have developed and fine-tuned this IG test. The IG test allows ascertaining a concentration of the formulation for which a gelled deposit is observed *in vitro* in presence of BSA in the concentration of 30mg/ml. BSA induces the gel formation in vitro during the IG test for obtaining the concentration C1, but BSA is not part of the composition itself.

Singh is directed to methods of controlling shipping fever or other adverse reactions in livestock by administration of IL - 2 and formulations of IL - 2 for controlled release (See Specification at col. 4, ll. 19 – 35). Singh et al., disclose formulations of PEGylated IL - 2 and human serum albumin (HSA) in a ratio of about 1:5 to about 1:30 by weight (See Specification at col. 6, ll. 2 - 5 and col. 13, ll. 45 – 60). Singh does not cure the deficiency of Huille relating to the critical concentration and the IG test.

More importantly, Singh discloses formulations which contain HSA or BSA. The composition of the current invention does not contain BSA. In Singh *et al.*, the release profile of the PEGylated IL - 2 is controlled by encapsulating the active principle mixed with HSA in microcapsules composed by poly(lactide-co-glycolide) excipient (See Specification at col. 4, l 26-31). In Singh's invention, HSA ensures the desirable release characteristics (See Specification at col. 5 and 6). In the same way, Akiyoshi and Hora provide evidence that the BSA acts in a matter to provide controlled release of the IL-2 in the composition. In contrast, the release profile of the current invention is controlled by the specific concentration of the polymer and not by HSA or BSA.

Further, the prior art Singh does not disclose how to find the right concentration of polymer by which the release is greatly increased. Furthermore, the microcapsules disclosed by Singh are different from the nanoparticles of the current invention in terms of size. To conclude, Singh combined with Huille does not teach to a person ordinary skill in the art how to have the right concentration of polymer PO to obtain the desirable release characteristics.

Lambert does not cure the deficiency of Huille relating to the critical concentration and the IG test. Lambert is directed to pharmaceutical compositions containing tocopherol, with and without an aqueous phase, a surfactant and a therapeutic agent (See Specification at col. 4, ll. 55 – 59). The tocopherol acts as a carrier for therapeutic drugs and can be used as a hydrophobic

dispersed phase of emulsions, a self emulsifying system, microemulsions or a PEGylated tocopherol (See Specification at col. 12, l. 56 - col. 13, l. 45).

Lambert does also not anticipate the existence of a critical concentration for which the release time is greatly increased. Additionally this document does not disclose how to perform a test in order to determine the 0.9 C1 critical concentration. The relation between an in vitro protein-induced gelling phenomenon, the critical concentration 0.9 C1 and a great increase in the release time was not anticipated. None of the references teach this relation and no combination of the prior art could prompted a person having ordinary skill in the art to use such a specific IG test. The combination of these references therefore cannot render the instant invention of claim 3 obvious. All other claims depend directly or indirectly from claim 3 and therefore, contain all the limitations of claim 3, and thus are not obvious.

For these reasons, Huille combined with Lambert, Singh, Akiyoshi and Hora, do not render the instant claims obvious. The applicants respectfully request the Examiner withdraw the rejection of claims 3 - 7, 9, 10, 12 - 15, 17 – 26, 35 - 40 and new claims 41 and 42 under 35 U.S.C. § 103(a) for allegedly being obvious in view of the prior art.

Obviousness - Type Double Patenting Rejections

The examiner rejects claims 3-7, 9, 10, 12-15, 18-22, 24, and 36-40, alleging they are obvious over claims 1-35 of Huille, as evidenced by the Handbook and Akioyshi. Applicants hereby incorporates the above arguments.

Huille does not teach the relation between an in vitro protein-induced gelling phenomenon, the critical concentration 0.9 C1 and a great increase in the release time of the Interleukin. Akiyoshi does not cure this deficiency. The combination of these references therefore cannot render the instant invention of claim 3 obvious. All other claims alleged by the examiner to depend directly or indirectly from claim 3 and therefore, contain all the limitations of claim 3, and thus are not obvious. Applicants therefore respectfully request to this rejection be withdrawn.

The Examiner also alleges that claims 3-7, 9-15, 17, and 21-26 are obvious over claims 3-7, 9-15, and 21-26 of the pending US application number 10/580,023 and claims 3-7, 9-15, 17, 21, 22 and 24-26 are obvious over claims 3-7, 9-15, and 21-26 of co-pending US application number 10/580,037. Applicants respectfully disagree. For sake of expediting prosecution, however, Applicants submit herewith a terminal disclaimer. Applicants therefore respectfully request withdrawal of the rejection.

Conclusion

In view of the foregoing amendments and remarks, the Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Applicants believe no fee is due with this submission. If a fee is due, however, the U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 022290.0158PTUS, from which the undersigned is authorized to draw.

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Respectfully submitted,

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